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(54) Title: SELF-ADHESIVE HYDRATABLE MATRIX FOR TOPICAL THERAPEUTIC USE

(57) Abstract: A self-adhesive, biocompatible and hydratable polymeric matrix has the form of a sheet, patch or film. The matrix is suitable for application to moist surfaces both inside and on the external surface of the body. The matrix comprises a naturally occurring or synthetic polymerisable and/or cross-linkable material that supports wound healing, and a synthetic polymer having bioadhesive properties. The bioadhesive properties enable the matrix to adhere to underlying tissue by means of ionic and/or hydrogen bonding.

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Title: - Sheet or the like, for topical therapeutic use

This invention relates to a sheet, patch or film for topical application to internal and external surfaces of the body, for therapeutic purposes. In particular, the invention relates to a self-adhesive, biocompatible and hydratable polymeric matrix, which may be used for wound healing, joining, sealing and reinforcing weakened tissue, and for drug delivery.

The use of therapeutic materials in the form of a sheet, patch or film, for topical administration to either internal or external organs of the body, is well documented for a wide range of medical applications. A disadvantage of currently available products is that they require manipulation *in situ* in order to secure the product in place, particularly internally. This manipulation commonly involves either mechanical attachment (eg using sutures) or chemical reaction with underlying tissue – either with the aid of externally applied energy (eg light or radio frequency energy) or though interaction between two or more of the components.

In many instances the use of sutures is either not wholly effective (eg on the lung), or undesirable as their introduction gives rise to further areas of tissue weakness. The use of external energy for attachment can be both time-consuming and (in some cases) requires significant careful judgement on the part of the surgeon, to evaluate when sufficient energy has been delivered to effect attachment without damaging the underlying tissue. Also, chemical interaction between components creates a risk of unwanted polymerisation and possible side effects of the reaction itself.

There has now been devised an improved form of sheet or the like, suitable for topical application, either internally or externally, that overcomes or substantially mitigates the above-mentioned or other disadvantages of the prior art.

According to the invention, there is provided a self-adhesive, biocompatible and hydratable polymeric matrix in the form of a sheet, patch or film suitable for application to moist surfaces both inside and on the external surface of the body, the matrix comprising a naturally occurring or synthetic polymerisable and/or cross-linkable material that supports wound healing, and a synthetic polymer having bioadhesive properties, such properties enabling the matrix to adhere to underlying tissue by means of ionic and/or hydrogen bonding.

The sheet or the like according to the invention is advantageous primarily in that the bioadhesive properties of the synthetic polymer enable the sheet to be positioned securely without the use of sutures or other forms of external physical attachment. The sheet is thus easy to use and can be applied rapidly and precisely.

The sheet or the like according to the invention may comprise in addition a therapeutically effective agent, ie a drug or medicament, and may be used as a delivery vehicle for such an agent. However, other embodiments of the invention are not used in this way, and are free of drug or medicament.

An important feature of the sheet or the like according to the invention is that it is suitable for application to both internal and external surfaces of the body, ie it may be applied topically to the exterior of the body (eg to the skin) or to internal surfaces such as surfaces of internal organs exposed during surgical procedures.

The polymerisable and/or cross-linkable component of the matrix is preferably selected from the polysaccharides, polylactates, polyalcohols and proteins, and derivatives thereof. The polymerisable component of the matrix may be partially or fully cross-linked.

In certain preferred embodiments of the invention, the polymerisable and/or cross-linkable component of the matrix is a protein or proteinaceous material, in

particular a protein or the like that can be cross-linked by the application of heat or electromagnetic energy (eg a structural protein such as collagen or a globular protein such as albumin).

A particularly preferred protein for use in the invention is albumin, particularly mammalian albumin such as porcine, bovine or human albumin.

In other preferred embodiments of the invention, the polymerisable and/or cross-linkable component of the matrix is a polysaccharide or a derivative thereof. Particular polysaccharides that may be mentioned include cellulose derivatives, particularly cellulose ethers and derivatives and salts thereof. Examples include carboxymethyl cellulose and salts thereof, hydroxypropylmethyl cellulose and hydroxyethylmethyl cellulose. Sodium carboxymethyl cellulose is one example of such a polymer.

The bioadhesive polymer component of the matrix may be any polymer with suitable bioadhesive properties, ie any polymer which confers on the matrix a sufficient degree of adhesion to the tissue to which it is applied. Such polymers typically contain chemical groups with a high ionic density, eg carboxyl, amide, hydroxyl, ether and ester groups, and the salts thereof, which interact cooperatively with tissue, through the formation of ionic and hydrogen bonds, dipole - dipole interactions and Van der Waals forces. Effective polymers are generally of high molecular weight since the degree of bioadhesion may be proportional to the number of these groups available. Typically, the molecular weight of the bioadhesive polymer will be in excess of about 100,000. The polymers are also generally linear, becoming physically entangled and having an amorphous distribution in solution. Preferably they should be able to be cross-linked to stabilise and strengthen the bioadhesive layer in the sheet, without compromising the bioadhesive properties. Examples of suitable polymers are poly(carboxylic acids) and their derivatives (ie polyanhydrides, polyesters),

copolymers of carboxylic acids and their derivatives, polyalcohols and their derivatives.

A preferred group of bioadhesive polymers are polymers consisting of recurring structural units containing amide groups. Preferably, the recurring unit is, or contains a 1-ethylenepyrrolidin-2-one (vinylpyrrolidone) group. Homopolymers containing recurring vinylpyrrolidone groups are particularly preferred, ie poly(vinylpyrrolidone).

The bioadhesive polymer may alternatively be a copolymer, eg a copolymer of amide-containing units as described above and carboxylic acid ester-containing units, eg vinyl acetate units. One particular form of copolymer that may be suitable is thus poly(vinylpyrrolidone)/poly(vinylacetate) copolymer.

Other groups of polymers that may exhibit suitable bioadhesive properties include polymers which may also serve as the polymerisable and/or cross-linkable component of the matrix, such as cellulose derivatives, particularly cellulose ethers and derivatives and salts thereof. Examples include carboxymethyl cellulose and salts thereof, hydroxypropylmethyl cellulose and hydroxyethylmethyl cellulose. Sodium carboxymethyl cellulose is again one example of such a polymer.

Combinations of polymers of the kinds described above may be employed. One preferred example is a combination of a polymer of amide-containing units as described above and a cellulose derivative as described above. A particular combination is poly(vinylpyrrolidone) and a salt, eg the sodium salt, of carboxymethyl cellulose. In such a combination, the polymer of amide-containing units, eg poly(vinylpyrrolidone), is preferably present in a proportion of between 0.1 and 60 times that of the cellulose derivative, more preferably between 1 and 40 times. The polymer of amide-containing units is preferably the predominant component, ie it is present in a greater proportion than the cellulose derivative.

Where the matrix comprises both a polymer of amide-containing units, eg poly(vinylpyrrolidone), and a cellulose derivative, eg carboxymethyl cellulose, certain embodiments may further comprise another polymerisable and/or cross-linkable material, most preferably a protein or proteinaceous material, eg albumin.

Sufficiency of the degree of adhesion of the matrix to the tissue, by the bioadhesive polymer(s), can be quantitatively determined *in vitro*, for example by performing a peel strength test. This test is performed by allowing the matrix to adhere to a suitable substrate (secured in a fixed position), while the matrix itself is physically attached at a separate point to the load of a tensile testing apparatus, positioned so that prior to the test, the matrix is not under load. The load cell is moveable along an axis substantially perpendicular to that along which the substrate is positioned. The test involves movement of the load cell away from the substrate, at a constant predetermined rate, until the matrix detaches from the substrate. The output of the test is a quantitative measure of the peel fracture energy for that matrix – ie the cumulative amount of energy required to break the interaction between the matrix and the substrate to which it is adhered. A suitable cumulative peel fracture energy for the matrix according to the invention would be not less than 10,000 N/m, more preferably not less than 20,000 N/m.

The matrix preferably further comprises a plasticiser in order to ensure that the matrix has sufficient flexibility, even after polymerisation or cross-linking. Suitable plasticisers include polyalcohols, eg glycerol, sorbitol etc.

The matrix may also comprises a synthetic or biological structural polymer to confer strength and elasticity on the matrix. Suitable polymers include water-soluble thermoplastic polymers, in particular selected from the group consisting of

poly(vinyl alcohol), poly(ethylene glycol), poly(acrylic acid), poly(acrylamide) and similar materials.

The bioadhesive polymer component of the matrix, eg poly(vinyl pyrrolidone), may also contribute to the structural properties of the matrix.

One or more surfactants, most preferably non-ionic surfactants, will generally be incorporated into the matrix, for instance to facilitate manufacture (eg to either prevent foaming, for production of closed structures, or to promote foaming, for the production of more mesh-like structures). Suitable surfactants include block copolymers of ethylene oxide and propylene oxide, such as those sold under the trade marks Pluronic® by BASF. In some instances, the proportion of surfactant incorporated into the matrix may be relatively low, eg less than 1%. In other embodiments, which have an open, mesh-like structure as described below, higher proportions of surfactants may be used, eg to create and stabilise a foam formed during manufacture.

The matrix in the form of a sheet, patch or film may be homogeneous or heterogeneous in composition, and may be of continuous or discontinuous structure. One or both major surfaces may have adhesive properties.

One group of preferred embodiments of the matrix according to the invention comprises the following proportions (percentages by weight) of the individual components:

a) polymerisable and/or cross-linkable material - from about 2% to 80% by weight, more preferably 5% to 60%, and most preferably 10% to 30%;

b) bioadhesive polymer(s) – from about 5% to 90% by weight, more preferably 20% to 80%, and most preferably 30% to 60%;

c) structural polymer – from about 0.01% to 20% by weight, more preferably 1% to 15%, and more preferably 2% to 10%;

d) surfactant – from about 0.001% to 10% more preferably 0.01% to 1%, and most preferably 0.01% to 0.1%;

e) plasticiser – from about 1% to 70%, more preferably 10% to 60%, and most preferably 20% to 40%.

The matrix may contain between 2% and 60% water by weight, and most preferably between 5% and 30%. The matrix may be partially or totally hydrated with a suitable aqueous medium at or following implantation (eg a body fluid or saline solution).

Other embodiments, eg those prepared by lyophilization as described below, may be substantially free of water.

The matrix may be manufactured by combining solutions of the different components as follows (all amounts are percentage weight of the component in the respective solution prior to combination):

a) Solution A:

i) polymerisable and/or cross-linkable material: 5 – 60%, more preferably 10 - 50%, and most preferably 20 – 40%.

ii) structural polymer : 0.1 – 30%, more preferably 1 – 20%, and most preferably 3 – 10%.

iii) surfactant : 0.001 – 5%, more preferably 0.01 – 1%, and most preferably 0.05– 0.5%.

iv) plasticiser : 1 – 80%, more preferably 10 – 60%, and most preferably 15 – 35%.

b) Solution B:

i) bioadhesive polymer(s) : 1 – 60%, more preferably 5 – 40%, and most preferably 10 – 30%.

ii) plasticiser :1 – 60%, more preferably 5 – 40%, and most preferably 10 – 30%.

In a preferred embodiment, where one surface only, or a selected part thereof, is bioadhesive, the matrix may be prepared by casting Solution A into a suitable non-stick mould (eg of PTFE), and causing or allowing it to set through evaporation. Onto this is then cast Solution B, which is also caused or allowed to set. During this process, the second solution penetrates into, and chemically binds to, the matrix formed by the first solution, so that the final matrix is composed of a single sheet with concentration gradients of the various components.

Alternatively, the matrix may be prepared from a single solution comprising all the components, or by combination of multiple solutions to create multi-lamellar matrices (eg bioadhesive – polymeric matrix – bioadhesive).

The casting process used to achieve the desired thickness of the sheet may involve pouring, manual spreading or spraying of the component solutions.

When prepared as described above, the matrix according to the invention may be 20 – 1000 μm in thickness, and typically approximately 100 - 500 μm in thickness. Dimensionally, the patch or film may have a surface area of only a few square millimetres, extending to several tens of centimetres.

For some uses, it may be desirable to modify the stability of the sheet – such that the half-life of the product is extended (for use in reinforcement of weakened tissue) or reduced (for drug release). This modification of stability can be effected by controlling the extent of formation of covalent bonds between molecules in the matrix (eg formation of disulphide bonds between protein

molecules). If an increase in patch stability is desired, the matrix can be pre-treated to induce the formation of intermolecular covalent bonds. The structural layer in particular may be partially or fully cross-linked.

Pre-treatment methods that can be used to modify the stability of the matrix are:

1) Heat : Heat may be used to partially or fully cross-link proteins and to drive off water from the bioadhesive component. Temperatures from 30-70°C will promote an unravelling of the polypeptide chains, which may reduce water solubility of the protein. Exposure of the matrix to temperatures between 70°C and 120°C will promote formation of covalent bonds between albumin molecules. This will increase the stability of the sheets, the degree of stability achieved being dependent on the precise time, and temperature of this pre-treatment.

2) Irradiation : Electromagnetic radiation (including visible and UV light, gamma irradiation and electron beam) can promote cross-linking of albumin molecules, and will polymerise the bioadhesive molecules. This is a potential method by which large sheets could be pre-treated in such a way as to increase their stability.

3) Chemical : There are a large variety of chemical cross-linking reagents which could potentially be used to induce formation of covalent bonds within the matrix, including chromophore dyes such as methylene blue.

In a particularly preferred embodiment the sheet or patch according to the invention is prepared from two or three separate layers, and the manufacture of the patch involves exposure to both heat and ionizing radiation. The structural layer containing a protein such as albumin is prepared first, and is partially or fully polymerised by exposure to heat for a given period of time. One or two additional bioadhesive layers are cast on top of the pre-formed structural layer – these are exposed to heat to evaporate off water, which may otherwise impede the

bioadhesive nature of the final product. The completed patch is packaged and gamma-irradiated which both achieves inter- and intra-molecular polymerisation of the bioadhesive layer and sterilization of the patch. The former is necessary to optimise strength of the bioadhesive layer and create a tightly bound structure that will not delaminate, while the latter is necessary for implantation within the body cavity.

In an alternative embodiment, the patch may be presented in a lyophilized form, (to improve stability and enhance its absorptive capacity). The process of lyophilization (which involves freezing the patch at between –20°C and –70°C, and subsequently exposing the frozen patch to a vacuum to remove residual water) must take place after exposure of the patch to electromagnetic radiation. The residual water in the patch may be partially or totally removed during this process in order to achieve the required degree of absorption and elasticity.

In a further, related embodiment the patch may be presented in the form of a sponge, being mesh-like, and evidently open in structure, with only a minor proportion of the overall volume of the structure being occupied by solid material. In this case the patch is manufactured and exposed to γ-irradiation, and then swollen in water or a buffer to the required degree. Other aqueous solutions can be used to swell the patch in order to include the solute in the final product. The swollen patch is finally freeze-dried as above, to remove some or all of the water.

Embodiments of the invention having open, mesh-like structures may comprise the following proportions (percentages by weight) of the individual components:

a) bioadhesive, polymerisable and/or cross-linkable material - from about 1% to 30% by weight, more preferably 5% to 30%, and most preferably 10% to 25%;

b) surfactant – from about 0.01% to 20%, more preferably 0.1% to 15%, and most preferably 1% to 15%;

c) plasticiser – from about 1% to 50%, more preferably 5% to 30%, and most preferably 10% to 25%.

Such embodiments may be manufactured by combining foamed solutions of the different components as follows (all amounts are percentage weight of the component in the respective solution prior to combination):

a) Solution A:

i) bioadhesive, polymerisable and/or cross-linkable material: 5 - 35%, more preferably 10-30%, and most preferably 20-30%.

ii) surfactant : 0.01-20%, more preferably 0.1-15%, and most preferably 1-15%.

b) Solution B:

i) bioadhesive, polymerisable and/or cross-linkable material : 1-30%, more preferably 5-30%, and most preferably 10-25%.

ii) plasticiser : 1-90%, more preferably 10-60%, and most preferably 10-50%.

iii) surfactant : 0.01-20%, more preferably 0.1-15%, and most preferably 1-15%.

The solutions A and B may be agitated to form foams, typically rather viscous in nature, which are then mixed. The resulting mixture may have the form of a gel. Prior to freeze-drying (lyophilization), the mixture or gel is preferably cross-linked (most preferably by exposure to ionizing radiation) and swollen in water or a buffer solution.

Further exposure to ionizing radiation may follow lyophilization, in order to achieve sterilization.

Such embodiments of the invention may be provided on one surface with a continuous coating of a synthetic or naturally occurring polymeric material. Such a material may, for instance, be a water-soluble thermoplastic polymer, in

particular selected from the group consisting of poly(vinyl alcohol), poly(ethylene glycol), poly(acrylic acid), poly(acrylamide) and similar materials.

According to a further aspect of the invention, there is therefore provided a process for the manufacture of a self-adhesive, biocompatible and hydratable polymeric matrix in the form of a sheet, patch or film suitable for application to moist surfaces both inside and on the external surface of the body, which process comprises forming a foamed solution of a naturally occurring or synthetic polymerisable and/or cross-linkable material that supports wound healing, and a synthetic polymer having bioadhesive properties, and subjecting said foamed solution to freeze-drying.

The process may comprise foaming a solution containing all the components of the matrix. Alternatively, the process may involve forming a first solution of the naturally occurring or synthetic polymerisable and/or cross-linkable material, and a second solution of the synthetic polymer having bioadhesive properties, foaming the first solution and the second solution, and then mixing the first and second solutions.

Manufacture of the matrix according to the invention is preferably carried out at reduced pH, preferably at a pH of less than 4.0, more preferably less than 3.0, eg about pH 2.0. Where the components of the matrix contain carboxy groups, eg where the matrix includes carboxymethyl cellulose, it is believed that the reduced pH increases the number of protonated carboxyl groups present. This in turn increases the hydrogen bonding capacity of the carboxyl groups (hydrogen bonding occurring for instance between the carboxyl groups of the carboxymethyl cellulose and carbonyl groups present in a polymer of recurring amide-containing units). This increased hydrogen bonding strengthens the polymer network of the gel, which in turn limits the degree of swelling that the gel undergoes. This provides benefits for the product in terms of ease of manufacturing, improved handling and improved structural integrity following implantation. Additionally,

manufacture and swelling at low pH may provide the product with advantageous efficacy properties such as a localised physiological environment optimised for triggering the blood clotting cascade, so leading to rapid haemostasis.

Where the manufacturing process involves the use of reduced pH, the solutions of the various components may be made up in a low pH buffer, rather than in water, and/or a reduced pH buffer may be used to swell the gel produced in the course of manufacture.

Embodiments of the invention prepared by freeze-drying of foamed solutions may have thicknesses of 0.1 to 10mm or more, typically 0.5 to 8mm, more commonly 0.5 to 5mm.

The sheet, patch or film according to the invention is particularly suitable for surgical applications in the following areas:

Thoracic / cardiovascular
General surgery
ENT
Urology
Oral / maxillofacial
Orthopaedic
Neurological
Gastroenterology
Ophthalmology
Gynaecology / obstetrics

Possible uses are described in more detail below.

Wound healing

The biodegradable nature of the sheet means that it may support and promote wound healing both during internal and topical procedures. Once the sheet begins to degrade fibroblasts will move in and begin to deposit components of the extracellular matrix. The sheet therefore can be used as an internal or external dressing. In addition, factors such as growth factors and cAMP that are known to promote the proliferation of skin cells may be added to the sheet to assist in the healing process. The sheet may act as a barrier to moisture and infectious agents, and thus be useful particularly in the treatment of burns.

Skin closure

The sheet may be applied topically to promote wound closure (as an alternative to sutures). This may have beneficial effects in that it may reduce scarring, and the sheet may thus be useful for cosmetic purposes during minor surgery (eg in Accident and Emergency Departments). The self-adhesive properties of the patch would make it easy to apply quickly.

Hernia repair

A 'stabilised' form of the sheet may be used to provide reinforcement in hernia repair procedures. The self-adhesive attachment overcomes the potential issues faced by conventional surgical reinforcing mesh products, which require suturing or stapling in an already weakened area. The patch for such a procedure may be engineered to have short or long term durability, depending on the degree of tissue repair required.

Anastomosis

The self-adhesive patch formulation described here provides a means of rapid sealing of, and prevention of leaks in, joined tubular structures such as blood vessels, and vascular and bladder grafts, and the GI tract. The ability of the patch to support tissue repair may be of particular value here if used in nerve repair.

Sealing large areas of tissue

The good sealing and dry / wet handling properties of the patch, combined with its self-adhesive properties and ability to be manufactured to cover a large surface area, mean that it may be of particular use in sealing resected tissue surfaces – in particular those where diffuse bleeding is an issue (eg the liver). The patch also provides an ideal support matrix for tissue repair at such sites. This could also be applicable to limiting leakage of cerebro-spinal fluid following neurological surgery.

Sealing air leaks

In addition to the patch properties described above, the high tensile strength and good inherent elasticity of the patch, make it particularly suitable for sealing air leaks in the lung, particularly following lung resection. Again, after effecting a seal, the patch provides an ideal support matrix for tissue repair at such sites.

Therapeutic agent administration

Drugs and other therapeutic agents (including biologically active agents such as growth factors, and even cellular components) may be added to the solution(s) used to form the patch product, or covalently linked to components prior to their use in patch formation. Once the patch is in place, following application to the desired site, the drug will be slowly released from the patch, either by diffusion out of the sheet, or by engineering the sheet so that as it degrades over time the drug is released. The rate of release can be controlled by appropriated design of the matrix. The patch thus provides a means of delivering a known amount of drug either systemically or to a precise locus. The drug may be directly bound to the protein, sandwiched between layers of the patch or simply dispersed in the matrix.

Prevention of Post-Surgical Adhesions

Post-surgical adhesion, the formation of undesired connective tissue between adjacent tissues, is a serious problem which can give rise to major post-surgical complications. It is a particular problem in bowel surgery where it can cause, for instance, twisting of the bowel which may then necessitate further surgical intervention. It has been found that the application of sheet material having self-adhesive properties in accordance with the invention to tissues exposed in a surgical procedure can be effective in preventing post-surgical adhesions between that tissue and neighbouring tissues.

Thus, according to another aspect of the invention there is provided a method for the prevention or inhibition of post-surgical adhesion, which method comprises applying to one or more tissues exposed in a surgical procedure a hydratable polymeric matrix in the form of a sheet, patch or film, the matrix comprising a naturally occurring or synthetic polymerisable and/or cross-linkable material and a synthetic polymer having bioadhesive properties.

A related aspect of the invention provides the use of a hydratable polymeric matrix in the form of a sheet, patch or film, the matrix comprising a naturally occurring or synthetic polymerisable and/or cross-linkable material and a synthetic polymer having bioadhesive properties, in the manufacture of a composition for the prevention or inhibition of post-surgical adhesion.

The invention will now be described in greater detail, by way of illustration only, with reference to the following Examples.

Example 1

Bilayer Hydrogel Patch

A solution in water comprising 28.6% porcine albumin, 17% glycerol, 5% PVA and 0.1% Pluronic 25R2 was cast onto a PTFE-coated flat surface and spread to

a thickness of 70μm. This solution was heated to 100 °C for 10 minutes and allowed to cool.

A second solution in water, comprising 9.6% PVP K-90D, 9.7% CMC90 and 9.5% glycerol was similarly cast on top of the previously formed layer, to a thickness of 600 μm. The matrix was heated further to 100 °C for 10 minutes, and again allowed to cool.

The resulting bilayer hydrogel patch (approximately 140 μm thickness) was cut to size and sealed inside foil pouches. The individual patches were subsequently γ-irradiated. In a study to evaluate the utility of these patches for sealing sutured anastomses against blood loss, a self-adhesive patch of size 2cm x 2cm was applied over end-to-end conventionally sutured carotid artery anastomoses in each of six rabbits. The animals were recovered and maintained for 21 days. Acute blood loss from anastomoses treated with the patches (mean = 0.14g) was significantly lower (p=0.011) than that of sutured alone controls (mean = 2.7g). Subsequent healing of the treated anastomoses was comparable to that of sutured only controls, demonstrating that the patch supported tissue repair and natural healing processes.

Example 2

Trilayer Hydrogel Patch

A solution in water comprising 28.3% porcine albumin, 18.1% glycerol, 5% PVA and 0.1% Pluronic 25R2, was cast onto a PTFE-coated flat surface and spread to a thickness of 140μm. This solution was heated to 100 °C for 10 minutes and allowed to cool.

A second solution in water, comprising 23.2% PVP K-90D and 12.6% glycerol, was similarly cast on top of the previously formed layer, also to a thickness of 140 μm. The matrix was heated further to 100 °C for 10 minutes, and again allowed to cool.

A third solution in water comprising 17.8% PVP K-90D, 9.7% glycerol and 0.01% CMC AF3285, was cast on to the second layer, and spread to a thickness of 600μm. The entire matrix was then heated to 100 °C for 15 minutes, and allowed to cool.

The resulting trilayer hydrogel patch (approximately 330 μm thickness) was cut to size and sealed inside foil pouches. The individual patches were subsequently γ-irradiated.

Separately a viscous hydrogel was formed, comprising PVP K90-D (9.8% w/w)), CMC-90 (9.4% w/w) and glycerol (9.5% w/w). This was filled into a syringe, sealed inside a foil pouch and γ-irradiated.

A preclinical study in rabbits was undertaken to evaluate the utility of the gel + self-adhesive patch for sealing tissue defects against blood loss. A 6 mm punch biopsy was performed in the liver of each of six animals. The gel was first applied to the wound to fill the injury, and then a 4 cm^2 self-adhesive patch was placed over the wound site, and allowed to adhere. The animals were recovered and maintained for 16 days. Acute blood loss from wound sites treated with the patches (mean = 1.3g) was significantly lower ($p=0.033$) than that of untreated controls (mean = 13.0g). Subsequent healing of patch + gel treated wounds was comparable to that of controls in which the wound was stabilised with the cellulose-based haemostat patch sold under the trade name Surgicel, demonstrating that the patch supported tissue repair.

Example 3

Bilayer Hydrogel Patch

A solution in water comprising 28.3% porcine albumin, 18.1% glycerol, 5% PVA and 0.1% Pluronic 25R2, was cast onto a PTFE-coated flat surface and spread to

a thickness of 210 µm. This solution was heated to 90 °C for 5 minutes and allowed to cool.

A second solution in water, comprising 13.2% PVP K-90D, 13.7% glycerol and 13.6% CMC-90, was similarly cast on top of the previously formed layer, to a thickness of 1200 µm. The matrix was heated further to 100 °C for 20 minutes, and again allowed to cool.

The resulting bilayer hydrogel patch (approximately 360 µm thickness) was cut to size and sealed inside foil pouches. The individual patches were subsequently γ-irradiated.

Separately a viscous hydrogel was formed, comprising PVP K90-D (9.8% w/w)), CMC-90 (9.4% w/w) and glycerol (9.5% w/w). This was filled into a syringe, sealed inside a foil pouch and γ-irradiated.

An acute preclinical study in rabbits was undertaken to evaluate the utility of the gel + self-adhesive patch for sealing tissue injury in the lung against air leak. A circular injury (approximately 10mm in diameter and 5mm deep) was made to a lung in each of five animals. The gel was first applied to the injury to fill the defect, and then a 4 cm^2 self-adhesive patch was placed over the wound site, and allowed to adhere to the underlying tissue. Each treated wound was observed for a maximum of 10 minutes. In all cases, air leak from the treated injury was markedly lower than in the untreated injury and in 3 cases, there was no air leak observed from the treated injuries.

Example 4

Freeze-Dried Bilayer Patch

A solution in water comprising 28.6% porcine albumin, 17% glycerol, 5% PVA and 0.1% Pluronic 25R2 was cast onto a PTFE-coated flat surface and spread to

a thickness of 70μm. This solution was heated to 100 °C for 10 minutes and allowed to cool.

A second solution in water, comprising 9.6% PVP K-90D, 9.7% CMC90 and 9.5% glycerol was similarly cast on top of the previously formed layer, to a thickness of 600 μm. The matrix was heated further to 100 °C for 10 minutes, and again allowed to cool.

The resulting bilayer patch was γ-irradiated (25 – 40 kGy) to achieve cross-linking. The patch was then frozen at –30°C for 12 hours. The samples were then freeze-dried at –20°C for 48 hours followed by 12 hours at 0°C and finally 24 hours at 25°C. The dried samples were terminally sterilised by γ-irradiation (25 – 40 kGy).

Example 5

Freeze-Dried Monolayer Patch

Solution A: Pluronic F-68 (2.5 g) and Pluronic F-127 (2.5 g) copolymers were added slowly to 68.5 g of water for injection stirred at 300 rpm. The same level of stirring was maintained until the copolymers were dissolved. The speed of the stirrer was increased to 2500 rpm to form a foam that was typically 4 times the volume of the original solution. Poly(vinyl pyrrolidone) K-90D (26.5 g) was then added to the vortex of the foam to avoid formation of lumps. The foamy viscous solution was left to settle for 12 hours before being used.

Solution B: Glycerol (12.6 g) was mixed with 69.9 g of water for injection using a rotor stirrer set at 300 rpm. Pluronic F-68 (2.5 g) and Pluronic F-127 (2.5 g) copolymers were added slowly to the water/glycerol solution and the same level of stirring was maintained until the copolymers were dissolved. The speed of the stirrer was increased to 2500 rpm to form a foam that was typically 4 times the volume of the original solution. Sodium carboxymethyl cellulose Blanose 7LF

(12.6 g) was then added to the vortex of the foam to avoid formation of lumps. The foamy viscous solution was left to settle for 12 hours before being used.

63 g of Solution B were thoroughly mixed with 37 g of solution A. The resultant gel was put into suitable moulds and γ-irradiated (25 - 40 kGy). This process produced a crosslinked gel that was then swollen in water for injection or pH 2 buffer (i.e. citric acid 0.03M/NaCl 0.061M/HCl 0.0082M) for 72 hours.

The swollen gels were transferred to trays and frozen at –30°C for 12 hours. The samples were then freeze-dried at –20°C for 48 hours followed by 12 hours at 0°C and finally 24 hours at 25°C. The dried samples were terminally sterilised by γ-irradiation (25 – 40 kGy).

Example 6

Freeze-Dried Monolayer Patch

Solution A: Pluronic F-68 (2.5 g) and Pluronic F-127 (2.5 g) copolymers were added slowly to 68.5 g of pH 2 buffer (i.e. citric acid 0.03M/NaCl 0.061M/HCl 0.0082M) stirred at 300 rpm. The same level of stirring was maintained until the copolymers were dissolved. The speed of the stirrer was increased to 2500 rpm to form a foam that was typically 4 times the volume of the original solution. Poly(vinyl pyrrolidone) K-90D (26.5 g) was then added to the vortex of the foam to avoid formation of lumps. The foamy viscous solution was left to settle for 12 hours before being used.

Solution B: Glycerol (12.6 g) was mixed with 69.9 g of pH 2 buffer (i.e. citric acid 0.03M/NaCl 0.061M/HCl 0.0082M) using a rotor stirrer set at 300 rpm. Pluronic F-68 (2.5 g) and Pluronic F-127 (2.5 g) copolymers were added slowly to the aqueous solution and the same level of stirring was maintained until the copolymers were dissolved. The speed of the stirrer was increased to 2500 rpm to form a foam that was typically 4 times the volume of the original solution. Sodium carboxymethyl cellulose Blanose 7LF (12.6 g) was then added to the

vortex of the foam to avoid formation of lumps. The foamy viscous solution was left to settle for 12 hours before being used.

63 g of Solution B were thoroughly mixed with 37 g of solution A. The resultant gel was put into suitable moulds and γ-irradiated (25 - 40 kGy). This process produced a crosslinked gel that was then swollen in water for injection or pH 2 buffer (i.e. citric acid 0.03M/NaCl 0.061M/HCl 0.0082M) for 72 hours.

The swollen gels were transferred to trays and frozen at –30°C for 12 hours. The samples were then freeze-dried at –20°C for 48 hours followed by 12 hours at 0°C and finally 24 hours at 25°C. The dried samples were terminally sterilised by γ-irradiation (25 – 40 kGy).

Example 7

Freeze-Dried Monolayer Patch

Solution A: Poly(vinyl alcohol) 80% hydrolysed (2.8 g) was added slowly to 70.4 g of water for injection stirred at 300 rpm, the same level of stirring was maintained until the polymer was dissolved. The speed of the stirrer was increased to 2500 rpm to form a foam that was typically 4 times the volume of the original solution. Poly(vinyl pyrrolidone) K-90D (26.8 g) was then added to the vortex of the foam to avoid formation of lumps. The foamy viscous solution was left to settle for 12 hours before being used.

Solution B: Glycerol (13 g) was mixed with 72.5 g of water for injection using a rotor stirrer set at 300 rpm. Poly(vinyl alcohol) 80% hydrolysed (1.5 g) was added slowly to the aqueous solution and the same level of stirring was maintained until the polymer was dissolved. The speed of the stirrer was increased to 2500 rpm to form a foam that was typically 4 times the volume of the original solution. Sodium carboxymethyl cellulose Blanose 7LF (13 g) was then added to the vortex of the foam to avoid formation of lumps. The foamy viscous solution was left to settle for 12 hours before being used.

62.6 g of Solution B were thoroughly mixed with 37.4 g of solution A. The resultant gel was put into suitable moulds and γ-irradiated (25 - 40 kGy). This process produced a crosslinked gel that was then swollen in water for injection or pH 2 buffer (i.e. citric acid 0.03M/NaCl 0.061M/HCl 0.0082M) for 72 hours.

The swollen gels were transferred to trays and frozen at –30°C for 12 hours. The samples were then freeze-dried at –20°C for 48 hours followed by 12 hours at 0°C and finally 24 hours at 25°C. The dried samples were terminally sterilised by γ-irradiation (25 – 40 kGy).

Example 8

Coated Freeze-Dried Patch

12 .5 g of poly(vinyl alcohol) 28-99 (Mw = 145000, 99 - 99.8% hydrolysed) were dissolved in 100 ml of water for injection at 95°C. The solution was allowed to cool down to room temperature.

5 x 5 cm samples of freeze-dried material prepared in Example 5 were uniformly coated with 0.5 ml of the above PVA 28-99 solution. The coated patches were put in a freezer set at -20°C for 12 hours. The samples were thawed at room temperature under vacuum and frozen at –20°C for another 12 hours. Finally, the patches were thawed to room temperature under vacuum, packed in aluminium foil pouches and terminally sterilised by γ-irradiation (25 – 40 kGy).

Claims

1. A self-adhesive, biocompatible and hydratable polymeric matrix in the form of a sheet, patch or film suitable for application to moist surfaces both inside and on the external surface of the body, the matrix comprising a naturally occurring or synthetic polymerisable and/or cross-linkable material that supports wound healing, and a synthetic polymer having bioadhesive properties, such properties enabling the matrix to adhere to underlying tissue by means of ionic and/or hydrogen bonding.

2. A matrix as claimed in Claim 1, which further comprises a drug or medicament, the matrix serving as a delivery vehicle for the drug or medicament.

3. A matrix as claimed in Claim 1, which is free of drug or medicament.

4. A matrix as claimed in any preceding claim, wherein the polymerisable and/or cross-linkable component of the matrix is selected from the polysaccharides, polylactates, polyalcohols and proteins.

5. A matrix as claimed in Claim 4, wherein the polymerisable and/or cross-linkable component of the matrix is a protein or proteinaceous material that can be cross-linked by the application of heat or electromagnetic energy.

6. A matrix as claimed in Claim 5, wherein the matrix comprises albumin.

7. A matrix as claimed in Claim 6, wherein the albumin is mammalian albumin such as porcine, bovine or human albumin.

8. A matrix as claimed in any one of Claims 1 to 3, wherein the polymerisable and/or cross-linkable component of the matrix is a polysaccharide or a derivative thereof.

9. A matrix as claimed in Claim 8, wherein the polysaccharide is a cellulose derivative.

10. A matrix as claimed in Claim 9, wherein the cellulose derivative is a cellulose ether or a derivative or a salt thereof.

11. A matrix as claimed in Claim 9, wherein the cellulose derivative is sodium carboxymethyl cellulose.

12. A matrix as claimed in any preceding claim, wherein the bioadhesive polymer component of the matrix contains carboxyl, amide, hydroxyl, ether or ester groups.

13. A matrix as claimed in Claim 12, wherein the bioadhesive polymer is selected from the group consisting of poly(carboxylic acids) and their derivatives, copolymers of carboxylic acids and their derivatives, and polyalcohols and their derivatives.

14. A matrix as claimed in Claim 12, wherein the bioadhesive polymer consists of recurring structural units containing amide groups.

15. A matrix as claimed in Claim 14, wherein the recurring unit is, or contains, a 1-ethylenepyrrolidin-2-one (vinylpyrrolidone) group.

16. A matrix as claimed in Claim 14, wherein the polymer is poly(vinylpyrrolidone).

17. A matrix as claimed in Claim 12, wherein the bioadhesive polymer is a copolymer of amide-containing units and carboxylic acid ester-containing units.

18. A matrix as claimed in Claim 17, wherein the copolymer is poly(vinylpyrrolidone)/poly(vinylacetate) copolymer.

19. A matrix as claimed in Claim 1, wherein the polymer having bioadhesive properties is a cellulose derivative.

20. A matrix as claimed in Claim 19, wherein the cellulose derivative is a cellulose ether or a derivative or a salt thereof.

21. A matrix as claimed in Claim 20, wherein the cellulose derivative is sodium carboxymethyl cellulose.

22. A matrix as claimed in Claim 1, which comprises a combination of a polymer of amide-containing units and a cellulose derivative.

23. A matrix as claimed in Claim 22, which comprises poly(vinylpyrrolidone) and a carboxymethyl cellulose derivative or salt thereof.

24. A matrix as claimed in Claim 23, which comprises sodium carboxymethyl cellulose.

25. A matrix as claimed in Claim 22, wherein the polymer of amide-containing units is present in a proportion of between 0.1 and 60 times that of the cellulose derivative.

26. A matrix as claimed in Claim 25, wherein the polymer of amide-containing units is present in a greater proportion than the cellulose derivative.

27. A matrix as claimed in any preceding claim, which has a peel fracture energy of not less than 10,000 N/m.

28. A matrix as claimed in any preceding claim, which further comprises a plasticiser.

29. A matrix as claimed in Claim 28, wherein the plasticiser is a polyalcohol.

30. A matrix as claimed in Claim 29, wherein the plasticiser is glycerol.

31. A matrix as claimed in any preceding claim, wherein the matrix further comprises a synthetic or biological structural polymer to confer strength and elasticity on the matrix.

32. A matrix as claimed in Claim 31, wherein the structural polymer is selected from the group consisting of poly(vinyl alcohol), poly(ethylene glycol), poly(acrylic acid), poly(acrylamide) and similar materials.

33. A matrix as claimed in any preceding claim, which further comprises one or more surfactants.

34. A matrix as claimed in Claim 33, which comprises a surfactant in the form of a copolymer of ethylene oxide and propylene oxide.

35. A matrix as claimed in Claim 1, which comprises:

a) polymerisable and/or cross-linkable material - from about 2% to 80% by weight, more preferably 5% to 60%, and most preferably 10% to 30%;

b) bioadhesive polymer(s) – from about 5% to 90% by weight, more preferably 20% to 80%, and most preferably 30% to 60%;

c) structural polymer – from about 0.01% to 20% by weight, more preferably 1% to 15%, and more preferably 2% to 10%;

d) surfactant – from about 0.001% to 10% more preferably 0.01% to 1%, and most preferably 0.01% to 0.1%;

e) plasticiser – from about 1% to 70%, more preferably 10% to 60%, and most preferably 20% to 40%.

36. A matrix as claimed in any preceding claim, which contains between 2% and 60% water by weight, and preferably between 5% and 30%.

37. A process for the manufacture of a matrix as claimed in any preceding claim, which process comprises forming solutions of the following compositions:

a) Solution A:

i) polymerisable and/or cross-linkable material: 5 – 60%, more preferably 10 - 50%, and most preferably 20 – 40%.

ii) structural polymer : 0.1 – 30%, more preferably 1 – 20%, and most preferably 3 – 10%.

iii) surfactant : 0.001 – 5%, more preferably 0.01 – 1%, and most preferably 0.05– 0.5%.

iv) plasticiser : 1 – 80%, more preferably 10 – 60%, and most preferably 15 – 35%.

b) Solution B:

i) bioadhesive polymer(s) : 1 – 60%, more preferably5 – 40%, and most preferably 10 – 30%.

ii) plasticiser :1 – 60%, more preferably 5 – 40%, and most preferably 10 – 30%.

and combining Solution A with Solution B.

38. A process as claimed in Claim 37, which further comprises casting Solution A in a mould and causing or allowing it to set by evaporation to form a first layer.

39. A process as claimed in Claim 38, further comprising casting Solution B onto the first layer.

40. A matrix as claimed in Claim 1, which has the form of a sponge, being mesh-like, and evidently open in structure, with only a minor proportion of the overall volume of the structure being occupied by solid material.

41. A matrix as claimed in Claim 40, which comprises:

a) bioadhesive, polymerisable and/or cross-linkable material - from about 1% to 30% by weight, more preferably 5% to 30%, and most preferably 10% to 25%;

b) surfactant – from about 0.01% to 20%, more preferably 0.1% to 15%, and most preferably 1% to 15%;

c) plasticiser – from about 1% to 50%, more preferably 5% to 30%, and most preferably 10% to 25%.

42. A matrix as claimed in Claim 40 or Claim 41, one surface of which has a continuous coating of a synthetic or naturally occurring polymeric material.

43. A process for the manufacture of a matrix as claimed in any one of Claims 40 to 42, which process comprises forming solutions of the following compositions:

a) Solution A:

i) bioadhesive, polymerisable and/or cross-linkable material: 5 - 35%, more preferably 10-30%, and most preferably 20-30%.

ii) surfactant : 0.01-20%, more preferably 0.1-15%, and most preferably 1-15%.

b) Solution B:

i) bioadhesive, polymerisable and/or cross-linkable material : 1-30%, more preferably 5-30%, and most preferably 10-25%.

ii) plasticiser : 1-90%, more preferably 10-60%, and most preferably 10-50%.

iii) surfactant : 0.01-20%, more preferably 0.1-15%, and most preferably 1-15%.

agitating the solutions A and B to form foams and mixing the solutions A and B to form a gel.

44. A process as claimed in Claim 43, which further comprises cross-linking of the gel.

45. A process as claimed in Claim 44, wherein the cross-linking is carried out by exposing the gel to ionizing radiation.

46. A process as claimed in any one of Claims 43 to 45, which further comprises swelling of the gel.

47. A process as claimed in any one of Claims 43 to 46, which further comprises freeze-drying of the gel.

48. A process for the manufacture of a self-adhesive, biocompatible and hydratable polymeric matrix in the form of a sheet, patch or film suitable for application to moist surfaces both inside and on the external surface of the body, which process comprises forming a foamed solution of a naturally occurring or synthetic polymerisable and/or cross-linkable material that supports wound healing, and a synthetic polymer having bioadhesive properties, and subjecting said foamed solution to freeze-drying.

49. A process as claimed in Claim 48, which comprises foaming a solution containing all the components of the matrix.

50. A process as claimed in Claim 48, which comprises forming a first solution of the naturally occurring or synthetic polymerisable and/or cross-linkable material, and a second solution of the synthetic polymer having bioadhesive properties, foaming the first solution and the second solution, and then mixing the first and second solutions.

51. A process as claimed in any one of Claims 43 to 50, which is carried out at reduced pH.

52. A process as claimed in Claim 51, which is carried out at a pH of less than 4.0.

53. A process as claimed in Claim 51, which is carried out at a pH of less than 3.0.

54. A process as claimed in any one of Claims 51 to 53, which involves forming one or more solutions in a low pH buffer.

55. A process as claimed in any one of Claims 51 to 54, which involves swelling of the gel in a low pH buffer.

56. A matrix as claimed in Claim 1, which has a thickness of 20 – 1000 μm.

57. A matrix as claimed in Claim 40, which has a thickness of 0.1 to 10mm.

58. A method for the prevention or inhibition of post-surgical adhesion, which method comprises applying to one or more tissues exposed in a surgical procedure a matrix as claimed in any one of Claims 1 to 36 or 40 to 42.

59. The use of a matrix as claimed in any one of Claims 1 to 36 or 40 to 42 in the manufacture of a composition for the prevention or inhibition of post-surgical adhesion.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB 01/04682

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/32 A61L31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 30405 A (FORTUNE DAVID HARRY; TISSUEMED LTD (GB); VELADA JOSE (GB)) 3 May 2001 (2001-05-03) page 1, line 30 -page 5, line 23 ---	1-59
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2002	08/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Heck, G

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 58 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

INTERNATIONAL SEARCH REPORT

Information on patent family members

In onal Application No
PCT/GB 01/04682

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DERWENT-ACC-NO: 2002-527408

DERWENT-WEEK: 200663

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TITLE: Self-adhesive, bio-compatible, hydratable-polymeric matrix sheet, useful for prevention or inhibition of post surgical adhesion, e.g. wound healing, comprises polymerizable and/or cross-linkable material and bio-adhesive synthetic polymer

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PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE
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AU 200195765 A	May 6, 2002	EN
EP 1328300 A1	July 23, 2003	EN
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AU 2001295765 B2	February 23, 2006	EN

DESIGNATED-STATES: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI S K SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR AT BE CH CY DE DK ES FI FR GB GR I E IT LI LU MC NL PT SE TR

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
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TYPE	IPC DATE
CIPP	A61K9/70 20060101
CIPP	A61L15/32 20060101
CIPS	A61K47/10 20060101
CIPS	A61K47/30 20060101
CIPS	A61K47/32 20060101
CIPS	A61K47/34 20060101
CIPS	A61K47/36 20060101
CIPS	A61K47/38 20060101
CIPS	A61K47/42 20060101
CIPS	A61K47/46 20060101
CIPS	A61L15/32 20060101
CIPS	A61L15/44 20060101
CIPS	A61L31/04 20060101
CIPS	A61L31/04 20060101

RELATED-ACC-NO: 2001-432482

ABSTRACTED-PUB-NO: WO 0234304 A1

BASIC-ABSTRACT:

NOVELTY - A self-adhesive, bio-compatible and hydratable polymeric matrix (I) as sheet, film or patch, comprises a naturally occurring or synthetic polymerizable and/or cross-linkable material and a synthetic polymer having bio-adhesive properties. The properties of polymer enable the matrix to adhere to underlying tissue by ionic and/or hydrogen bonding.

DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) A process for the manufacture of a matrix, comprises formation of:

(a) Solution A, comprises (%):

(i) polymerizable and/or cross-linkable material (5-60, preferably 20-40);

(ii) structural polymer (0.1-30, preferably 3-10);

(iii) surfactant (0.001-5, 0.05-0.5); and

(iv) plasticizer (1-80, preferably 15-35); and

(b) Solution B, comprises:

(i) bio-adhesive polymer(s) (1-60, preferably 10-30); and

(ii) plasticizer (1-60, preferably 10-30);

(2) A method for prevention or inhibition of post-surgical adhesion, which involves applying (I) to one or more tissues exposed in a surgical procedure; and

(3) Use of (I) in the manufacture of a composition for the prevention or inhibition of post-surgical procedure.

None given.

USE - (I) is used in the manufacture of a composition for prevention and/or inhibition of post surgical adhesion (claimed).

For application to moist surfaces both inside and on the external surface of the body for wound healing, joining, sealing and reinforcing weakened tissue such as hernia and anastomosis and for drug delivery in various areas such as thoracic/cardiovascular, general surgery, ear nose and throat, urology, oral/ maxillofacial, orthopedic, neurological,

gastroenterology, ophthalmology, gynecology/obstetrics.

ADVANTAGE - The bio-adhesive properties of the synthetic polymer enable the sheet to be positioned securely without the use of sutures or other forms of external physical attachment, thus the sheet is easy to use and can be applied rapidly and precisely.

EQUIVALENT-ABSTRACTS:

PHARMACEUTICALS

Preferred Composition: The matrix either comprises or is free of a drug or medicament, and serves as a delivery vehicle for the drug.

POLYMERS

Preferred components: The polymerizable and/or cross-linkable components of the matrix are polysaccharides or derivatives, polylactates, polyalcohols and/or proteins or proteinaceous material that can be cross-linked by the application of heat or electromagnetic energy. The polysaccharide is a cellulose ether or salt derivative such as sodium carboxymethyl cellulose.

The matrix comprises albumin. The albumin is mammalian albumin such as porcine, bovine or human albumin.

The bio-adhesive polymer component of the matrix contains carboxyl, amide, hydroxyl ether or ester groups. Bio-adhesive polymers are poly(carboxylic acids) and their derivatives, copolymer of carboxylic acids and their derivatives, and polyalcohols and their derivatives. The bio-adhesive polymer consists of recurring structural units containing amide groups, where the recurring unit is 1-ethylenepyrrolidin-2-one (vinylpyrrolidone) group, preferably the polymer is poly (vinyl pyrrolidone). The polymer is a copolymer of amide-containing units and carboxylic acid ester-

containing units. The copolymer is poly (vinylpyrrolidone)/Poly(vinyl acetate)copolymer.

The amide containing unit is present in a ratio of 0.1-60 times that of the cellulose derivative.

Preferred Properties: The matrix has a peel fracture energy of not less than 10,000 N/M.

The plasticizer in the matrix is polyalcohol or glycerol.

The polymer further comprises a synthetic or biological structural polymer to confer strength and elasticity on the matrix. The structural polymer is poly(vinyl alcohol), poly(ethylene glycol), poly(acrylic acid), ploy(acrylamide) and similar materials. The surfactant in the matrix is in the form of a copolymer of ethylene oxide and propylene oxide. The matrix has a thickness of 20-1000 mum.

Preferred Composition: The matrix comprises (in weight %):

(i) polymerizable and/or cross-linkable material (2-8, preferably 10-30);

(ii) bio-adhesive polymer(s) (5-90, preferably 30-60);

(iii) structural polymer (0.01-20, preferably 2-10);

(iv) surfactant (0.001-10, preferably 0.01-0.1);

(v) plasticizer (1-70, preferably 20-40); and

(vi) water (2-60, preferably 5-30).

Preferred Method: Solution A is cast in a mold to allow it to set and form a first layer. Then solution B is cast onto the first layer. The matrix formed is sponge-

like and evidently open in structure with only a minor proportion of the overall volume of the structure occupied by solid material. The matrix surface is coated with a synthetic or naturally occurring polymeric material.

Solutions A and B are mixed to form a gel and the gel is cross-linked by exposing to ionizing radiation. The pH of the solutions is reduced to less than 3.0 and the gel is swelled in the low pH buffer. The gel is swelled and freeze-dried.

A solution in water containing (in %) porcine albumin (28.6), glycerol (17), polyvinyl acetate (PVA) (5) and Pluronic 25R2 (RTM) (0.1) was cast onto a polytetrafluoroethylene-coated flat surface and spread to a thickness of 70 mum. The solution was heated to 100 degreesC for 10 minutes and allowed to cool.

A second solution in water, containing PVP K-90D (RTM) (9.6), CMC90 (RTM; carboxy methyl cellulose) (9.7) and glycerol (9.5) was similarly cast on top of the previously formed layer, to a thickness of 600 mum.

The matrix was heated to 100 degreesC for 10 minutes, and again allowed to cool to obtained a bilayer hydrogel patch.

TITLE-TERMS: SELF ADHESIVE BIO COMPATIBLE HYDRATED POLYMERISE MATRIX SHEET USEFUL PREVENT INHIBIT POST SURGICAL WOUND HEAL COMPRISE CROSS LINK MATERIAL SYNTHETIC POLYMER

DERWENT-CLASS: A96 B04 D22 G03 P31 P34

CPI-CODES: A12-V01; A12-V03A; B04-C02A2; B04-C03; B04-F02; B04-N02; B05-A01B; B07-A03; B10-E04C; B12-M02D; B14-N17B; D09-C04B;

CHEMICAL-CODES: Chemical Indexing M1 *01*
Fragmentation Code M423 M430 M781 M782
P942 Specific Compounds RA0121
Registry Numbers 184614

Chemical Indexing M1 *02*
Fragmentation Code M423 M430 M781 M782
P942 Specific Compounds RA00I9
Registry Numbers 184613

Chemical Indexing M1 *03*
Fragmentation Code M423 M430 M781 M782
P942 Specific Compounds RA00H3
Registry Numbers 184616

Chemical Indexing M1 *04*
Fragmentation Code M423 M430 M781 M782
P942 Specific Compounds R24039
Registry Numbers 86886

Chemical Indexing M1 *05*
Fragmentation Code A111 A960 C710 H5
H521 H8 J0 J011 J1 J171 M280 M311 M321
M342 M349 M381 M391 M423 M430 M630
M781 M782 P942 Specific Compounds
R07352 RA0GUZ Registry Numbers 133912
133998 140011 140012 190069

Chemical Indexing M1 *06*
Fragmentation Code F012 F013 F423 H7
H715 H721 J5 J521 L9 L941 M210 M212
M240 M281 M320 M423 M430 M510 M521
M530 M540 M781 M782 P942 Specific
Compounds RA00D5 Registry Numbers 1062

Chemical Indexing M6 *07*
Fragmentation Code P942 R041 R043 R111
R112 R210 R220

UNLINKED-DERWENT-REGISTRY-NUMBERS: ; 1835U

ENHANCED-POLYMER-INDEXING:

Polymer Index [1.1]
018 ; G3623*R P0599 D01 G3634*R D03 D11 D10 D23 D22 D31 D42 D76 F24 F34 H0293 G3623 G3678*R G3634; G3678 G3634 G3623 D01 D03 D11 D10 D23 D22 D31 D42 D50 D61 D76 D92 F24 F34 F38 F35 Na 1A H0293 P0599 R07352 R06717 133912 133998; M9999 M2073; S9999 S1365; S9999 S1309*R;

Polymer Index [1.2]
018 ; G2108 D01 D11 D10 D50 D60 D83 F27 F26 F36 F35 R00009 7447; P1978*R P0839 D01 D50 D63 F41; H0000; H0011*R; M9999 M2073; S9999 S1365; S9999 S1309*R;

Polymer Index [1.3]
018 ; D01 F26*R; P0000; M9999 M2073; S9999 S1365; S9999 S1309*R;

Polymer Index [1.4]
018 ; D01 F26*R; P0000; M9999 M2073; S9999 S1365; S9999 S1309*R;

Polymer Index [1.5]
018 ; G3714 P0599 D01 F70 R24039 86886; M9999

M2073; S9999 S1365;
S9999 S1309*R;

Polymer Index [1.6]
018 ; D01 D60 F35*R
F70*R F26*R F34 F41*R
D63; P0000; M9999
M2073; S9999 S1365;
S9999 S1309*R;

Polymer Index [1.7]
018 ; G0635 G0022 D01
D12 D10 D23 D22 D31 D41
D51 D53 D58 D75 D86
F71; G0566 G0022 D01
D11 D10 D12 D51 D53 D58
D63 D84 F41 F89 R00835
829; H0022 H0011;
H0044*R H0011; M9999
M2073; S9999 S1365;
S9999 S1309*R;

Polymer Index [1.8]
018 ; P1707 P1694 D01;
M9999 M2073; S9999
S1365; S9999 S1309*R;

Polymer Index [1.9]
018 ; G1558 D01 D23 D22
D31 D42 D50 D73 D82 F47
R00351 444; P8004 P0975
P0964 D01 D10 D11 D50
D82 F34; P0055; H0000;
M9999 M2073; S9999
S1365; S9999 S1309*R;

Polymer Index [1.10]
018 ; G0282 G0271 G0260
G0022 D01 D12 D10 D26
D51 D53 D58 D60 D83 F36

F35 R00446 1911; G0453
G0260 G0022 D01 D12 D10
D26 D51 D53 D58 D83 F70
F93 R00444 8781; H0000;
M9999 M2073; S9999
S1365; S9999 S1309*R;
P0088; P0099;

Polymer Index [1.11]
018 ; Q9999 Q6644*R;
Q9999 Q8059 Q7987;
ND01; B9999 B4988*R
B4977 B4740; N9999
N5743; N9999 N6440*R;
B9999 B5243*R B4740;
K9574 K9483; K9676*R;

Polymer Index [1.12]
018 ; G1070 G0997 D01
D11 D10 D50 D83 F29 F26
R00113 490; A999 A384;

Polymer Index [1.13]
018 ; A999 A566*R;

Polymer Index [2.1]
018 ; G1558 D01 D23 D22
D31 D42 D50 D73 D82 F47
R00351 444; G1558 D01
D11 D10 D23 D22 D31 D42
D50 D73 D83 F47 R00370
238; P0975*R P0964 F34
D01 D10; P0055; H0022
H0011; A999 A566*R;
A999 A782;

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CPI Secondary Accession Numbers: 2002-149318

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